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(54) Title: ANTIBIOTIC COMPOSITION WITH INHIBITOR

(57) Abstract: Antibiotic composition having four dosage forms with different release profiles providing for initial release of a beta lactam antibiotic followed by release of a beta-lactamase inhibitor, followed by release of the antibiotic followed by release of the inhibitor. In a preferred embodiment, release from the second, third and fourth dosage forms is initiated after the component released from the immediately previous form reaches C_{max} .

ANTIBIOTIC COMPOSITION WITH INHIBITOR

This application claims the priority of United States Provisional Application No. 60/184,582, filed on February 24, 2000.

This invention relates to antibiotics that contain beta-lactam rings that are subject to attack by beta-lactamases in combination with beta-lactamase inhibitors.

Antibiotics with beta-lactam rings, for example, penicillins and cephalosporins, are susceptible to attack from the beta-lactamases (sometimes called penicillinases) that will chemically inactivate the antibiotic. Clavulanic acid, and its derivatives, as well as sulbactam are generally used to bind irreversibly to the beta-lactamase to prevent its activity against such an antibiotic. Typically, there is provided an antibiotic composition that includes the inhibitor with such combinations generally being delivered as an immediate release dosage form.

The present invention relates to an improved antibiotic composition that is comprised of at least four different dosage forms, two of which include at least one antibiotic with a beta-lactam ring (or any portions of such a ring) and two of which include at least one beta-lactamase inhibitor, with the four different dosage forms

having release profiles such that there is a first dosage form that releases said at least one antibiotic, a second dosage form that releases at least one beta-lactamase inhibitor, a third dosage form that releases said at least one antibiotic, and a fourth dosage form that releases said at least one inhibitor, with the release profile of the first and second dosage forms being such that the maximum serum concentration of the inhibitor is reached at a time no sooner and preferably after the time at which the maximum serum concentration of the antibiotic released from the first dosage form is achieved, with the third dosage form having a release profile such that the second antibiotic achieves a maximum serum concentration at a time no sooner than and preferably after the time at which the inhibitor released from the second dosage form reaches a maximum serum concentration, and with the fourth dosage form having a release profile such that the maximum serum concentration of the inhibitor released from the fourth dosage form is achieved at a time no sooner and preferably after a time that the maximum serum concentration is reached for the at least one antibiotic released from the third dosage form.

In one preferred embodiment, the initiation of release from the second, third and fourth dosage form occurs at least one hour after initiation of release from the first, second and third form, respectively.

In a preferred embodiment of the present invention, a maximum serum concentration for the antibiotic released from the first dosage form is achieved in no more than about three hours; the maximum serum concentration for the inhibitor released from the second dosage form is reached in a time of from about three to six hours; the maximum serum concentration of the antibiotic released from the third dosage form is reached in from about six to nine hours, and the maximum serum concentration released from the fourth dosage form is achieved in no more than

twelve hours, with such times being measured from the time of administration of the antibiotic composition that is comprised of the at least four different dosage forms.

In a preferred embodiment of the present invention, the at least four dosage forms are provided with release profiles such that the inhibitor is released from the second dosage form after the maximum serum concentration is achieved for antibiotic released from the first dosage form; antibiotic is released from the third dosage form after the maximum serum concentration is reached for the inhibitor released from the second dosage form, and inhibitor is released from the fourth dosage form after the maximum serum concentration is reached for the antibiotic released from the third dosage form.

It is to be understood that when it is disclosed herein that a dosage form initiates release after another dosage form, such terminology means that the dosage form is designed and is intended to produce such later initiated release. It is known in the art, however, notwithstanding such design and intent, some "leakage" of antibiotic or inhibitor may occur. Such "leakage" is not "release" as used herein.

Although, in a preferred embodiment there are four dosage forms, it is possible to have more than four dosage forms, provided that there is successive alternate release of antibiotic and inhibitor, and each inhibitor release achieves a serum concentration maximum no sooner than and preferably after the serum concentration maximum of the immediately preceding antibiotic released, and the next antibiotic released reaches a serum concentration maximum no sooner than and preferably after the serum concentration maximum is achieved for the immediately preceding inhibitor dosage form.

In an embodiment of the present invention each of the dosage forms that contains an inhibitor includes such inhibitor in an amount that is effective to inhibit

chemical inactivation of the antibiotic by beta-lactamase. In general, the dosage forms that contain the inhibitor contain such an inhibitor in an amount from about 20 percent to about 80 percent.

Similarly, the dosage forms that contain the antibiotic generally include the antibiotic in an amount from about 30 percent to about 80 percent. Each of the dosage forms that deliver antibiotics include from 30% to 70% of the dosage of the antibiotic to be delivered by the composition.

In accordance with a preferred embodiment, the first dosage form that releases antibiotic is an immediate release dosage form. The second, third, and fourth dosage forms are delayed release dosage forms, which may be pH independent or pH dependent (enteric) dosage forms. The second, third and fourth dosage forms are formulated in a manner to provide the release profiles as hereinabove described.

At least four different dosage forms can be formulated into the overall antibiotic composition of the present invention, by procedures generally known in the art. For example, each of the dosage forms may be in the form of a pellet or a particle, with pellet particles being formed into the overall composition, in the form, for example, of the pellet particles in a capsule, or the pellet particles embedded in a tablet or suspended in a liquid suspension.

The antibiotic composition of the present invention may be administered, for example, by any of the following routes of administration: sublingual, transmucosal, transdermal, parenteral, and preferably are administered orally. The composition includes a therapeutically effective amount of the antibiotic, which amount will vary with the antibiotic to be used, the disease or infection to be treated, and the number of times that the composition is to be delivered in a day.

The antibiotic product of the present invention, as hereinabove described, may be formulated for administration by a variety of routes of administration. For example, the antibiotic product may be formulated in a way that is suitable for topical administration; administration in the eye or the ear; rectal or vaginal administration; as nose drops; by inhalation; as an injectable; or for oral administration. In a preferred embodiment, the antibiotic product is formulated in a manner such that it is suitable for oral administration.

For example, in formulating the antibiotic product for topical administration, such as by application to the skin, the antibiotic may be formulated for topical administration by including such dosage forms in an oil-in-water emulsion, or a water-in-oil emulsion. In such a formulation, the immediate release dosage forms are in the continuous phase, and the delayed release dosage form is in a discontinuous phase. For example, there may be provided an oil-in-water-in-oil-in-water emulsion, with oil being a continuous phase that contains the immediate release component, water dispersed in the oil containing a first delayed release dosage form, and oil dispersed in the water containing a second delayed release dosage form, and water dispersed in the oil containing a third delayed release dosage form.

It is also within the scope of the invention to provide an antibiotic product in the form of a patch, which includes different antibiotic and inhibitor dosage forms having different release profiles, as hereinabove described.

Furthermore, the antibiotic product with different dosage forms with different release profiles may be formulated for rectal or vaginal administration, as known in the art. This may take the form of a cream or emulsion, or other dissolvable dosage forms similar to those used for topical administration.

As a further embodiment, the antibiotic product may be formulated for use in inhalation therapy by coating the particles and micronizing the particles for inhalation.

In a preferred embodiment, the antibiotic product is formulated in a manner suitable for oral administration. Thus, for example, for oral administration, each of the dosage forms may be used as a pellet or a particle, with a pellet or particle then being formed into a unitary pharmaceutical product, for example, in a capsule, or embedded in a tablet, or suspended in a liquid for oral administration.

Alternatively, in formulating an oral delivery system, each of the dosage forms of the product may be formulated as a tablet, with each of the tablets being put into a capsule to produce a unitary antibiotic product. Thus, for example, antibiotic products may include a first dosage form in the form of a tablet that is an immediate release tablet, and may also include three additional tablets, each of which provides for a delayed release of the antibiotic and inhibitor, as hereinabove described.

As hereinabove described, the antibiotics that are employed in the present invention are ones that include a beta-lactam ring or a portion thereof such as for example, penicillin derivatives, such as penicillin V, penicillin G, penicillin, ampicillin, amoxicillin, carbenicillin, ticarcillin, piperacillin, nafcillin, cloxacillin, dicloxacillin, monobactams such as aztreonam, carbapenems such as imipenem, cephalosporins such as cefoxitan, cephalexin, ceferioxone, cefuroxime, cefpodoxime, and others.

The beta-lactamase inhibitors maybe any one of a wide variety that are effective to inhibit the action of beta-lactamases on a beta-lactam ring, such as clavulanic acid and its derivatives, sulbactam.

In one embodiment, the product contains sufficient antibiotic for a twenty-four hour period whereby the product is administered once a day.

The Immediate Release Component

The immediate release portion of this system can be a mixture of ingredients that breaks down quickly after administration to release the antibiotic. This can take the form of either a discrete pellet or granule that is mixed in with, or compressed with, the other three components.

The materials to be added to the antibiotics for the immediate release component can be, but are not limited to, microcrystalline cellulose, corn starch, pregelatinized starch, potato starch, rice starch, sodium carboxymethyl starch, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, ethylcellulose, chitosan, hydroxychitosan, hydroxymethylatedchitosan, cross-linked chitosan, cross-linked hydroxymethyl chitosan, maltodextrin, mannitol, sorbitol, dextrose, maltose, fructose, glucose, levulose, sucrose, polyvinylpyrrolidone (PVP), acrylic acid derivatives (Carbopol, Eudragit, etc.), polyethylene glycols, such a low molecular weight PEGs (PEG2000-10000) and high molecular weight PEGs (Polyox) with molecular weights above 20,000 daltons.

It may be useful to have these materials present in the range of 1.0 to 60% (W/W).

In addition, it may be useful to have other ingredients in this system to aid in the dissolution of the drug, or the breakdown of the component after ingestion or administration. These ingredients can be surfactants, such as sodium lauryl sulfate, sodium monoglycerate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, glyceryl monostearate, glyceryl monooleate, glyceryl monobutyrate, one of the non-

ionic surfactants such as the Pluronic line of surfactants, or any other material with surface active properties, or any combination of the above.

These materials may be present in the rate of 0.05-15% (W/W).

The Delayed Release Component

The components in this composition are the same immediate release unit, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

Materials that can be used to obtain a delay in release suitable for this component of the invention can be, but are not limited to, polyethylene glycol (PEG) with molecular weight above 4,000 daltons (Carbowax, Polyox), waxes such as white wax or bees wax, paraffin, acrylic acid derivatives (Eudragit), propylene glycol, and ethylcellulose.

Typically these materials can be present in the range of 0.5-25% (W/W) of this component.

The Enteric Release Component

The components in this composition are the same as the immediate release component, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

The kind of materials useful for this purpose can be, but are not limited to, cellulose acetate phthalate, Eudragit L, and other phthalate salts of cellulose derivatives.

These materials can be present in concentrations from 4-20% (W/W).

The present invention will be described with respect to the following examples; however, the scope of the invention is not to be limited thereby. Unless

otherwise stated, all parts and percentages set forth in this specification are by weight.

Examples**Immediate Release Component**

	<u>Ingredient</u>	<u>Conc. (% W/W)</u>
Example 1:	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20
	Povidone	10
	Croscarmellose sodium	5
Example 2:	Amoxicillin	55% (W/W)
	Microcrystalline cellulose	25
	Povidone	10
	Croscarmellose sodium	10
Example 3:	Amoxicillin	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Hydroxypropylcellulose	5
Example 4:	Amoxicillin	75% (W/W)
	Polyethylene glycol 8000	20
	Polyvinylpyrrolidone	5
Example 5:	Clarithromycin	65% (W/W)
	Microcrystalline cellulose	20
	Hydroxypropylcellulose	10
	croscarmellose sodium	5
Example 6:	Clarithromycin	75 % (W/W)
	Microcrystalline cellulose	15
	Hydroxypropylcellulose	5
	croscarmellose sodium	5
Example 7:	Clarithromycin	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Hydroxypropylcellulose	5
Example 8:	Clarithromycin	75% (W/W)
	Polyethylene glycol 8000	20
	Polyvinylpyrrolidone	5
Example 9:	Ciprofoxacin	65% (W/W)
	Microcrystalline cellulose	15
	Hydroxypropylcellulose	5
	Croscarmellose sodium	5

Example 10:	Ciprofoxacin	75% (W/W)
	Microcrystalline cellulose	15
	Hydroxypropylcellulose	5
	Croscarmellose sodium	5
	Delayed Release Component	
Example 11:	Ciprofoxacin	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Hydroxypropylcellulose	5
Example 12:	Ciprofoxacin	75% (W/W)
	Polyethylene glycol 8000	20
	Polyvinylpyrrolidone	5
Example 13:	Ceftibuten	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Hydroxypropylcellulose	5
Example 14:	Ceftibuten	75% (W/W)
	Polyethylene glycol 4000	20
	Polyvinylpyrrolidone	5
Example 15:	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20
	Cellulose Acetate Pthalate	15
Example 16:	Amoxicillin	55% (W/W)
	Microcrystalline cellulose	25
	Cellulose Acetate Pthalate	10
	Hydroxypropylmethylcellulose	10
Example 17:	Amoxicillin	65 % (W/W)
	Polyox	20
	Hydroxypropylcellulose pthalate	10
	Eudragit E30D	5
Example 18	Amoxicillin	75% (W/W)
	Polyethylene glycol 2000	10
	Eudragit E30D	10
	Eudragit RL 30D	5
Example 19:	Amoxicillin	40% (W/W)
	Microcrystalline Cellulose	40
	Cellulose Acetate Pthalate	10
Example 20:	Clarithromycin	70% (W/W)
	Hydroxypropylcellulose pthalate	15
	Croscarmellose sodium	10

Example 21:	Clarithromycin	70% (W/W)
	Eudragit E30D	15
	Hydroxypropylcellulose	10
	Ethylcellulose	5
Example 22:	Clarithromycin	75% (W/W)
	Polyethylene glycol 2000	10
	Eudragit E 30D	15
Example 23:	Clarithromycin	40% (W/W)
	Lactose	50
	Eudragit E 30D	10
Example 24:	Ciprofoxacin	65% (W/W)
	Microcrystalline Cellulose	20
	Eudragit E 30D	10
Example 25	Ciprofoxacin	75% (W/W)
	Microcrystalline Cellulose	15
	Hydroxypropylcellulose pthalate	10
Example 26	Ciprofoxacin	80% (W/W)
	Lactose	10
	Eudragit E 30D	10
Example 27	Ciprofoxacin	70% (W/W)
	Polyethylene glycol 4000	20
	Cellulose acetate pthalate	10
Example 28	Ceftibuten	60% (W/W)
	Polyethylene Glycol 2000	10
	Lactose	20
	Eudragit E 30D	10
Example 29	Ceftibuten	70% (W/W)
	Microcrystalline Cellulose	20
	Cellulose acetate pthalate	10
Example 30:	Clavulanate potassium	65% (W/W)
	Microcyrstalline cellulose	20
	Cellulose Acetate Pthalate	15
Example 31:	Clavulanate potassium	55% (W/W)
	Microcrystalline cellulose	25
	Cellulose Acetate Pthalate	10
	Hydroxypropylmethlycellulose	10

Example 32:	Clavulanate potassium	65% (W/W)
	Polyox	20
	Hydroxypropylcellulose pthalate	10
	Eudragit E 30D	5
Example 33:	Clavulanate potassium	75% (W/W)
	Polyethylene glycol 2000	10
	Eudragit E30D	10
	Eudragit RL 30D	5
Example 34	Clavulanate potassium	40% (W/W)
	Microcrystalline cellulose	40
	Cellulose Acetate Pthalate	10
Example 35:	Clavulanate potassium	70% (W/W)
	Hydroxypropylcellulose pthalate	15
	Croscarmellose sodium	10
Example 36:	Clavulanate potassium	70% (W/W)
	Eudragit E30D	15
	Hydroxypropylcellulose pthalate	10
	Ethylcellulose	5
Example 37:	Clavulanate potassium	75% (W/W)
	Polyethylene glycol 2000	10
	Eudragit E 30D	15
Example 38:	Clavulanate potassium	40% (W/W)
	Lactose	50
	Eudragit E 30D	10
Example 39:	Clavulanate potassium	65% (W/W)
	Microcrystalline Cellulose	20
	Eudragit E 30D	10
Example 40:	Sulbactam	75% (W/W)
	Microcrystalline cellulose	15
	Hydroxypropylcellulose pthalate	10
Example 41:	Sulbactam	80% (W/W)
	Lactose	10
	Eudragit E 30D	10
Example 42:	Sulbactam	70% (W/W)
	Polyethylene glycol 4000	20
	Cellulose acetate pthalate	10

Example 43:

Sulbactam	60% (W/W)
Polyethylene glycol 2000	10
Lactose	20
Eudragit E 30D	10

Example 44:

Sulbactam	70% (W/W)
Microcrystalline cellulose	20
Cellulose Acetate phthalate	10

Example 45:

Clavulanate potassium	65% (W/W)
Microcrystalline cellulose	20
Polyox	10
Croscarmellose Sodium	5

Example 46:

Clavulanate potassium	55% (W/W)
Microcrystalline cellulose	25
Polyox	10
Glyceryl monooleate	10

Example 47:

Clavulanate potassium	65% (W/W)
Polyox	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 48:

Clavulanate potassium	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 49:

Clavulanate potassium	75% (W/W)
Polyethylene glycol 4000	20
Ethylcellulose	5

Example 50:

Clavulanate potassium	70% (W/W)
Polyox	20
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 51:

Clavulanate potassium	75% (W/W)
Polyox	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 52:

Clavulanate potassium	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 53:	Clavulanate potassium	80% (W/W)
	Polyethylene glycol 8000	10
	Polyvinylpyrrolidone	5
	Eudragit R.30D	5
Example 54:	Sulbactam	65% (W/W)
	Polyethylene glycol 4000	10
	Hydroxypropylcellulose	5
	Eudragit RL 30D	5
Example 55:	Sulbactam	75% (W/W)
	Microcrystalline cellulose	15
	Hydroxypropylcellulose	5
	Ethylcellulose	5
Example 56:	Sulbactam	80% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	5
	Eudragit RL 30D	5
Example 57:	Sulbactam	75% (W/W)
	Polyethylene glycol 8000	20
	Ethylcellulose	5
Example 58:	Sulbactam	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Eudragit RL 30D	5
Example 59:	Sulbactam	75% (W/W)
	Polyethylene glycol 8000	20
	Ethylcellulose	5

Example 60.**1 Beta Lactam Antibiotic and Beta-Lactamase Inhibitor Matrix Pellet****Formulation and Preparation Procedure****60.1 Pellet Formulation**

The composition of the antibiotic or inhibitor matrix pellets provided in Table 1.

Table 1 Composition of Antibiotic Pellets

Component	Percentage (%)
Antibiotic or Inhibitor	50
Avicel PH 101	20
Lactose	20
PVP K29/32*	10
Purified Water	
Total	100

*PVP K29/32 was added as a 20% w/w aqueous solution during wet massing.

60.2 Preparation Procedure for Antibiotic or Inhibitor Matrix Pellets

60.2.1 Blend antibiotic or inhibitor and Avicel® PH 101 using a Robot Coupe high shear granulator.

60.2.2 Add 20% Povidone K29/32 binder solution slowly into the powder blend under continuous mixing.

60.2.3 Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.

60.2.4 Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

60.2.5 Dry the spheronized pellets at 50°C overnight.

60.2.6 Pellets between 16 and 30 Mesh were collected for further processing.

60.2.7 The above procedure is used to prepare pellets that contain an antibiotic and pellets that contain an inhibitor.

60.3 Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion

60.3.1 Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the antibiotic matrix pellets and to the inhibitor matrix pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	55.0
Triethyl Citrate	1.6

Talc	8.0
Purified Water	37.4
Solids Content	25.5
Polymer Content	15.9

60.4 Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

60.4.1 Suspend triethyl citrate and talc in deionized water.

60.4.2 The TEC/talc suspension is then homogenized using a PowerGen 700 high shear mixer.

60.4.3 Add the TEC/talc suspension slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

60.4.4 Allow the coating dispersion to stir for one hour prior to application onto the antibiotic matrix pellets.

60.5 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

60.5.1 Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the inhibitor matrix pellets is provided below in Table 3.

Table 3 Eudragit® S 100 Aqueous Coating Dispersion

Component ¹	Percentage (%)
Part A	
Eudragit® S 100	12.0
1 N Ammonium Hydroxide	6.1
Triethyl Citrate	6.0
Purified Water	65.9
Part B	
Talc	2.0
Purified Water	8.0
Solid Content	20.0
Polymer Content	12.0

60.6 Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

- 60.6.1 Dispense Eudragit® S 100 powder in deionized water with stirring.
- 60.6.2 Add ammonium hydroxide solution drop-wise into the dispersion with stirring.
- 60.6.3 Allow the partially neutralized dispersion to stir for 60 minutes.
- 60.6.4 Add triethyl citrate drop-wise into the dispersion with stirring. Stir for about 2 hours prior to the addition of Part B.

Part B:

- 60.6.5 Disperse talc in the required amount of water
- 60.6.6 Homogenize the dispersion using a PowerGen 700D high shear mixer.
- 60.6.7 Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

60.7 Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters are used for coating with each of the Eudragit® L 30 D-55 and Eudragit® S 100 aqueous film coatings.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed
Coater	
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.8 Bar
Pump Rate	2 gram per minute

- 60.7.1 Coat matrix pellets with L30 D-55 dispersion such that you apply 12% coat weight gain to the pellets.
- 60.7.2 Coat matrix pellets with L30 D-55 dispersion such that you apply 30% coat weight gain to the pellets.
- 60.7.3 Coat matrix pellets with S100 dispersion such that you apply 20% coat weight gain to the pellets.

60.8 Encapsulation of the Antibiotic and Inhibitor Pellets

Pellets are filled into size 00 hard gelatin capsules at a ratio of 20%: 30%: 20%: 30% Immediate-release matrix pellets (uncoated), L30 D-55 coated pellets 12% weight gain, L30D-55 coated pellets 30% weight gain and S100 coated pellets respectively. The capsule is filled with the four different pellets to achieve the desired dosage.

The immediate release pellets contain the antibiotic; the L30 D-55 12% weight gain coated pellets contain the inhibitor; the L30 D-55 30% weight gain coated pellets contain the antibiotic and the S100 coated pellets contain the inhibitor.

The present invention is advantageous in that the beta-lactamase inhibitor will be dosed at a lower peak concentration, giving rise to fewer side effects. The alternative dosing of the antibiotic and the inhibitor will alternate the exposure to the bacteria in such a way as to make the antibiotic more effective than if they were co-administered, and thereby competing with each other for sites on the bacterial cell wall receptors.

Numerous modifications and variations of the present invention are possible in light of the above teachings, therefore, within the scope of the appended claims, the invention may be practiced otherwise than as particularly described.

What is claimed is:

1. An antibiotic composition comprising:

a mixture of at least four dosage forms, said first dosage form comprising at least one antibiotic with a beta-lactam ring or portion thereof and a pharmaceutically acceptable carrier; the second dosage form comprising at least one beta-lactamase inhibitor and a pharmaceutical carrier; the third dosage form comprising at least one antibiotic including a beta-lactam ring or portion thereof, and a pharmaceutically acceptable carrier; the fourth dosage form comprising at least one beta-lactamase inhibitor and a pharmaceutical carrier, said first dosage form and said second dosage form having release profiles whereby the maximum serum concentration of the inhibitor released from the second dosage form is reached at a time no sooner than the maximum serum concentration is reached for the antibiotic released from the first dosage form, the third dosage form having a release profile such that maximum serum concentration of the antibiotic released from the third dosage form is reached at a time no sooner than the time at which the maximum serum concentration for the inhibitor released from the second dosage form is achieved, and the fourth dosage form having a release profile whereby the inhibitor released from the fourth dosage form achieves a maximum serum concentration at a time that is no sooner than the time at which the maximum serum concentration of the antibiotic released from the third dosage form is achieved.

2. The antibiotic of Claim 1 wherein the second dosage form initiates release of inhibitor at least one hour after initiation of release of antibiotic from the first dosage form, the third dosage form initiates release of antibiotic at least one hour after initiation of release of inhibitor from the second dosage form and the

fourth dosage form initiates release of inhibitor at least one hour after initiation of release of antibiotic from the third dosage form.

3. The antibiotic of Claim 1 wherein the first dosage form is an immediate release dosage form.

4. The antibiotic of Claim 1 wherein the inhibitor is released from the second dosage form after the antibiotic released from the first dosage form reaches maximum serum concentration, the antibiotic is released from the third dosage form after the inhibitor released from the second dosage form reaches maximum serum concentration and inhibitor is released from the fourth dosage form after antibiotic released from the third dosage form reaches maximum serum concentration.

5. The antibiotic of Claim 1 wherein the composition includes the dosage of antibiotic for a twenty-four hour period.

6. The antibiotic of Claim 1 wherein the antibiotic composition is an oral dosage form.

7. The antibiotic of Claim 1 wherein the first dosage form includes from 30% to 80% of the antibiotic delivered by the composition and the remainder of the antibiotic is delivered by the fourth dosage form.

8. The antibiotic of Claim 4 wherein the first dosage form is an immediate release dosage form.

9. The antibiotic of Claim 8 wherein the composition includes the dosage of antibiotic for a twenty-four hour period.

10. The antibiotic of Claim 9 wherein the first dosage form includes from 30% to 80% of the antibiotic delivered by the composition and the remainder of the antibiotic is delivered by the fourth dosage form.

11. A process for treating a patient comprising treating the patient by administration of the antibiotic of Claim 1.

12. A process for treating a patient comprising treating the patient by administration of the antibiotic of Claim 2.

13. A process for treating a patient comprising treating the patient by administration of the antibiotic of Claim 3.

14. A process for treating a patient comprising treating the patient by administration of the antibiotic of Claim 4.

15. A process for treating a patient comprising treating the patient by administration of the antibiotic of Claim 5.

16. A process for treating a patient comprising treating the patient by administration of the antibiotic of Claim 6.

17. A process for treating a patient comprising treating the patient by administration of the antibiotic of Claim 7.

18. A process for treating a patient comprising treating the patient by administration of the antibiotic of Claim 8.

19. A process for treating a patient comprising treating the patient by administration of the antibiotic of Claim 9.

20. A process for treating a patient comprising treating the patient by administration of the antibiotic of Claim 10.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/05984

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/20, 9/54, 31/43, 31/545

US CL : 424/458, 464; 514/199, 200

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/458, 464; 514/199, 200

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96/04908 A1 (SMITHKLINE BEECHAM PLC) 22 February 1996 (22.02.96), see abstract, pages 1-3, claims 1-16.	1-20
Y	US 6,027,748 A (CONTE et al.) 22 February 2000 (22.02.00), column 14, lines 10-40, column 3, lines 30-50.	1-20
Y	WO 98/22091 A1 (YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM) 28 May 1998 (28.05.98), abstract, pages 29-31.	1-20

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.*** Special categories of cited documents:**

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